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PRIMARY DERMAL IRRITATION OF
1-ACETVLOCTAHYDRO-357-TRINITRO-1357-TETRAZINE(U)
LETTERMAN ARMY INST OF RESEARCH PRESIDIO OF SAN
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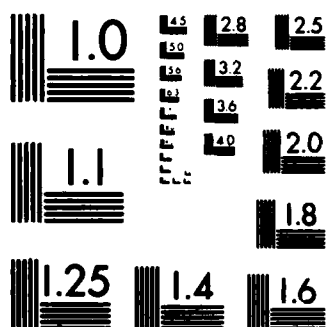
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INSTITUTE REPORT NO. 148

PRIMARY DERMAL IRRITATION OF 1-Acetyloctahydro-3,5,7-Trinitro-1,3,5,7-Tetrazine

CAROLYN M. LEWIS, MS

TOXICOLOGY GROUP,
DIVISION OF RESEARCH SUPPORT

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Toxicology Series 51

LETTERMAN ARMY INSTITUTE OF RESEARCH
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**Primary Dermal Irritation of 1-Acetyloctahydro-3,5,7-Trinitro-
1,3,5,7-Tetrazine (Toxicology Series 51)--Lewis**

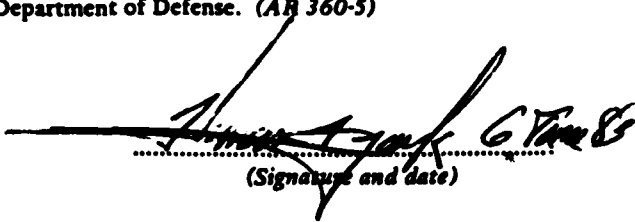
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4. TITLE (and Subtitle) Primary Dermal Irritation of 1-Acetyloctahydro-3,5,7-Trinitro-1,3,5,7-Tetrazine (SEX)		5. TYPE OF REPORT & PERIOD COVERED Final 17 Dec 82 - 31 Jan 83
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18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Primary Dermal Irritation, 1-acetyloctahydro-3,5,7-trinitro-1,3,5,7-tetrazine, SEX		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The explosives by-product, 1-acetyloctahydro-3,5,7-trinitro-1,3,5,7-tetrazine (SEX), was tested for primary dermal irritation potential on rabbits. The study was conducted in compliance with the Good Laboratory Practice Regulations. No erythema or edema was observed during the study; therefore, SEX was classified as a non-irritating chemical.		

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ABSTRACT

The explosives by-product, 1-acetyloctahydro-3,5,7-trinitro-1,3,5,7-tetrazine (SEX), was tested for primary dermal irritation potential on rabbits. The study was conducted in compliance with the Good Laboratory Practice Regulations. No erythema or edema was observed during the study; therefore, SEX was classified as a non-irritating chemical.



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PREFACE

TYPE REPORT: Primary Dermal Irritation GLP Study Report

TESTING FACILITY: US Army Medical Research and Development Command
Letterman Army Institute of Research
Division of Research Support
Presidio of San Francisco, CA 94129

SPONSOR: US Army Medical Research and Development Command
US Army Medical Bioengineering Research
and Development Laboratory
Fort Detrick, MD 21701

PROJECT: 612720.835AA, Acute Mammalian Toxicology Testing,
APC TL06

GLP STUDY NUMBER: 82006

STUDY DIRECTOR: COL John T. Fruin, DVM, PhD, VC, Diplomate of
American College of Veterinary Preventive Medicine

PRINCIPAL INVESTIGATOR: Carolyn M. Lewis, MS, DAC

REPORT AND DATA MANAGEMENT: A copy of the final report, study protocols,
raw data, retired SOPs and aliquot of the
test compound will be retained in the LAIR
Archives.

TEST SUBSTANCE: 1-Acetyloctahydro-3,5,7-Trinitro-1,3,5,7-
Tetrazine (SEX)

INCLUSIVE STUDY DATES: 22 December - 31 January 1983

OBJECTIVE: To evaluate the primary dermal irritation potential of
1-acetyloctahydro-3,5,7-trinitro-1,3,5,7-tetrazine (SEX).

ACKNOWLEDGMENTS

The authors wish to thank SP4 Thomas Kellner, BS; SP4 Lawrence Mullen, BS, and SP4 Evelyn Zimmerman for their assistance in the weighing, dosing and care of the animals. We also wish to thank CPT Craig White, VC, for his assistance in chemical handling and preparation, and CPT Martha Hanes, VC, for her advice on the conduct of the study. In addition, we wish to thank Jesse Barkley Jr., US Army Medical Bioengineering Research and Development Laboratory, for his assistance as Project Consultant.

SIGNATURES OF PRINCIPAL SCIENTIST AND MANAGERS INVOLVED IN THE STUDY:

We, the undersigned, believe the study number 82006 described in this report to be scientifically sound and the results in this report and interpretation to be valid. The study was conducted to comply, to the best of our ability, with the Good Laboratory Practice Regulations for Medical Laboratory Studies, outlined by the Food and Drug Administration.

John T. Fruin 13 Apr 83
JOHN T. FRUIN / DATE
COL, VC
Study Director

Carolyn M. Lewis 8 Apr 83
CAROLYN M. LEWIS, MS / DATE
DAC
Principal Investigator



DEPARTMENT OF THE ARMY
LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

REPLY TO
ATTENTION OF:

3GRD-ULZ-QA

2 May 1983

MEMORANDUM FOR RECORD

SUBJECT: Report of GLP Compliance

I hereby certify that in relation to LAIR GLP study 82006, the following inspections were made:

6 Jan 83, 1030 hours
6 Jan 83, 1545 hours
10 Jan 83, 0935 hours
10 Jan 83, 1025 hours
11 Jan 83

The report and raw data for this study were audited on 29 Apr 83.

Routine inspections with no adverse findings are reported quarterly, thus these inspections are also included in the April 83 report to management and the Study Director.

NELSON R. POWERS, Ph.D.
CPT, MSC
Quality Assurance Officer

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PRIMARY DERMAL IRRITATION OF 1-Acetyloctahydro-3,5,7-Trinitro-1,3,5,7-Tetrazine--Lewis

The manufacture of the explosives hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) and octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazine (HMX) at the Holston Army Ammunition Plant (HSAAP) results in the unavoidable formation of the by-product, 1-acetyloctahydro-3,5,7-trinitro-1,3,5,7-tetrazine (SEX). It is formed during nitrolysis of hexamine. During this process, a portion of the hexamine is also acetylated by the acetic acid/acetic anhydride solvent. As a result, significant quantities of SEX are discharged from HSAAP. HSAAP is the only known producer of SEX. Its discharge, while partially mitigated by present and planned pollution abatement facilities at HSAAP, will continue and could increase at mobilization. The information on the chemical, physical and toxicological properties of SEX is limited. Many of its properties can be inferred only by comparison to those of RDX and HMX. SEX appears to be more water soluble than RDX or HMX, although no specific values are available. Thus SEX could be more available to aquatic life than RDX or HMX and may exhibit a highly toxic effect on the organisms in the Holston River. The present study represents the first in a series of toxicological studies to be conducted at the Letterman Army Institute of Research (LAIR) to assess the toxicological hazards of SEX.

Objective of Study

The objective of the study is to evaluate the primary dermal irritation potential of 1-Acetyloctahydro-3,5,7-Trinitro-1,3,5,7-Tetrazine (SEX).

METHODS

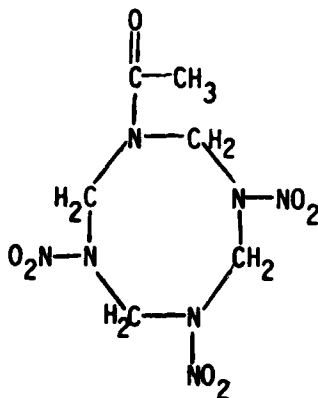
Test Substance

Chemical name:

1-Acetyloctahydro-3,5,7-Trinitro-1,3,5,7-Tetrazine

Chemical Abstract Service Registry No. 139800-00-2

Structural formula:



Empirical formula: C₆H₁₁N₇O₇

Chemical Data appear in Appendix A.

Animal Data

Animal Data appear in Appendix B.

Environmental Conditions

Environmental Conditions are listed in Appendix C.

Dosing

The backs of six rabbits were close-clipped and divided into four quadrants designated I,II,III and IV (1,2). Areas I and IV were intact on all animals and Areas II and III were abraded by making two perpendicular scratches in the stratum corneum of the skin about 1 1/2 inches long with a scarifier (3). The four application sites were about 10 cm apart. From Neter and Wasserman (4) 4 x 4 standard Latin squares were used to assign chemicals randomly to sites (SOP OP-STX-34). Each animal had two sites that were treated with the test compound. The third site was treated with the vehicle and the fourth was left untreated. A dose of 0.5 g solid test compound was used on each site. For the vehicle control a dose of 0.5 ml isotonic saline was used. The test compound was made into a paste using isotonic saline, then placed on a 1-inch square gauze patch which was then taped to the appropriate site. After all the patches were applied, a plastic strip was wrapped around the animal and then held in place with elastic tape to retard evaporation and insure skin contact with the test compound. The test compound was left in contact with the skin for 24 hours. At the end of the exposure period the wrapping and patches were removed, the skin was wiped if the material was adherent and the areas were scored.

Duration of Study

The study period was 21 days with an 18-day quarantine period before the study onset.

Appendix D is a historical listing of events.

Deviation from Original Protocol

Appendix E contains explanations of deviations from the original protocol.

RESULTS

Animals were scored at 24 hours, 72 hours, 7 days, 14 days, and 21 days after dosing for erythema and edema. The scale for scoring appears in Table 1. The average scores from 24 and 72 hours were used to determine the primary dermal irritation index. Abraded areas (sites II and III) and intact areas (sites I and IV) were graded separately and together. Tabular scoring data for 24 and 72 hours appear in Appendix F.

The primary irritation index was used as a basis for categorization (Category assignment and interpretation, personal communication, A.H. McCreesh, 1980). Non-irritating compounds (Category I) meet the following two criteria: 1) Combined (intact and abraded sites) indices of 2.00 or less and 2) intact indices of 0.50 or less. Mild irritants (Category II) have combined indices from 0.51 to 2.0, with the intact index greater than 0.50. Category III compounds are moderately irritating with combined indices between 2.1 and 5.0. Chemicals are considered severe irritants (Category IV) if they have combined indices between 2.1 and 7.9 and they produce necrosis, vesticulation, ulceration, and/or eschars. Compounds which are impossible to classify because of staining or masking of effects due to physical properties are placed in Category V.

No erythema or edema was ever observed with the test compound on intact or abraded skin. Nor was there any erythema or edema on intact or abraded skin when it was treated with saline or untreated (patch only). However, at the 24-hour observation some slight erythema was noted where the patch tape was in contact with the skin on all of the animals. The tape used was a surgical hypoallergenic tape (Transpore[®]) and was considered the most suitable tape for applying the patch. Since this tape-induced erythema was seen on all sites, regardless of its treatment, the erythema was not included in the score. Only the area immediately under the patch was used in the scoring. Taking these factors into consideration, the primary irritation index tabulated for SEX on both intact and abraded skin was zero. Therefore, SEX was classified as a non-irritating chemical (category I).

TABLE 1
EVALUATION OF SKIN REACTIONS (2)

Erythema and Eschar Formation

No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate-to-severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injurious in depth)	4
Possible total erythema score:	4*

Edema Formation

No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (edges raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Possible total edema score	4*

Possible total score for primary irritation	8
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* Any skin reaction more serious than severe erythema, severe edema, vesiculation, ulceration, or necrosis places the chemical in Category IV.

DISCUSSION

The test compound, 1-acetyloctahydro-3,5,7-trinitro-1,3,5,7-tetrazine (SEX), was classified as a non-irritating chemical based on the findings from the primary dermal irritation test (1,2). In order for a compound to be irritating it first must be absorbed through the skin (5). Most of the SEX was still present on the skin when the patches were removed after 24 hours. This suggests that very little, if any, of the compound was absorbed. The poor absorption of SEX was probably the main reason for it being non-irritating. The poor absorption of SEX, in turn, was probably due to its insolubility in water and many organic solvents. However, if a solvent such as acetone in which SEX is slightly soluble was used, it is possible some irritation might have been observed.

CONCLUSION

The test compound, 1-acetyloctahydro-3,5,7-trinitro-1,3,5,7-tetrazine (SEX) is non-irritating as categorized by findings from the primary dermal irritation test.

RECOMMENDATION

While SEX did not prove to be irritating when made into a paste with saline, it is possible that different results may be obtained if a solvent, such as acetone, is used in which SEX is slightly soluble. For this reason, another test with acetone or DMSO as the vehicle is recommended.

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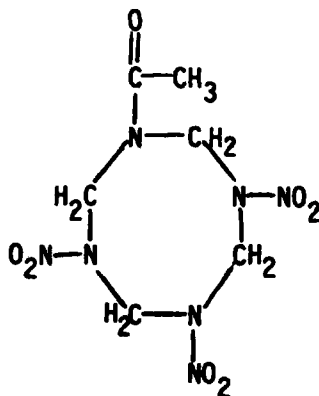
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CHEMICAL DATA

Chemical name: 1-Acetyloctahydro-3,5,7-Trinitro-1,3,5,7-Tetrazine

Chemical Abstract Service Registry No.: 139800-00-2

Structural formula:



Empirical formula: $C_6H_{11}N_7O_7$

Molecular weight: 293.2 g/mole (calculated). Typical experimental values Rast camphor method - 207 to 377 g/mole.

Physical state: Solid at 20 C

Melting Point: 224.2 - 224.7 C

Density: 1.785 g/cc at 21 C

pH: N/A nonaqueous

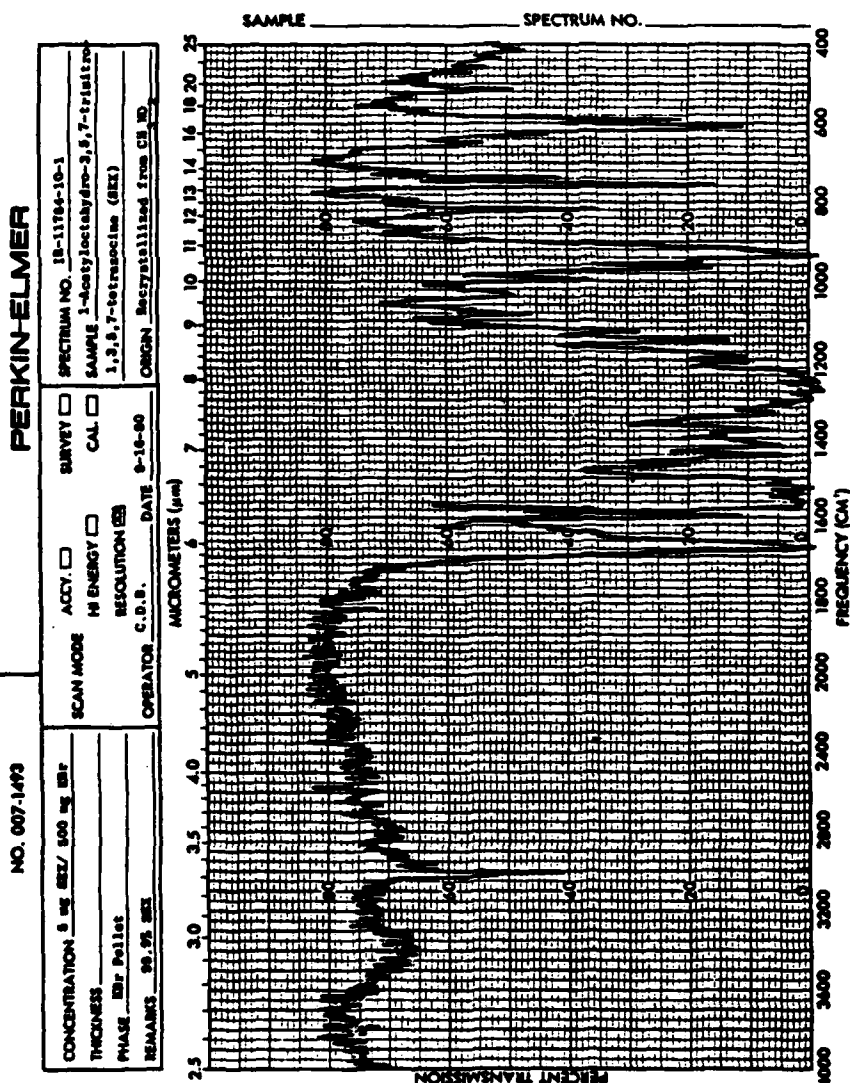
Compound Refractory Index: Unknown

Stability: Decomposes at 232 C (printout from differential scanning calorimeter attached). After 72 hours at 75 C there was no change in composition (IR, NMR and color) or weight loss.

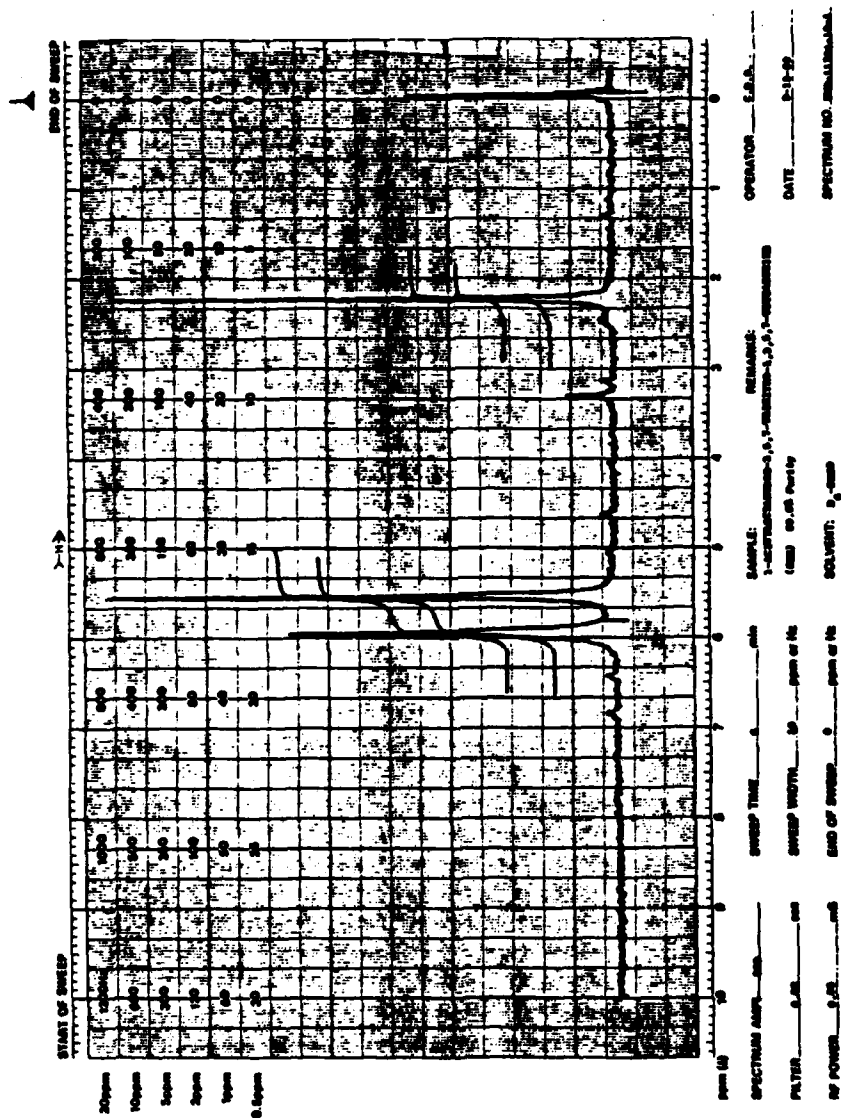
Purity: 99.9% IR and NMR spectra attached

Manufacturer: SRI, International
Menlo Park, CA 94205

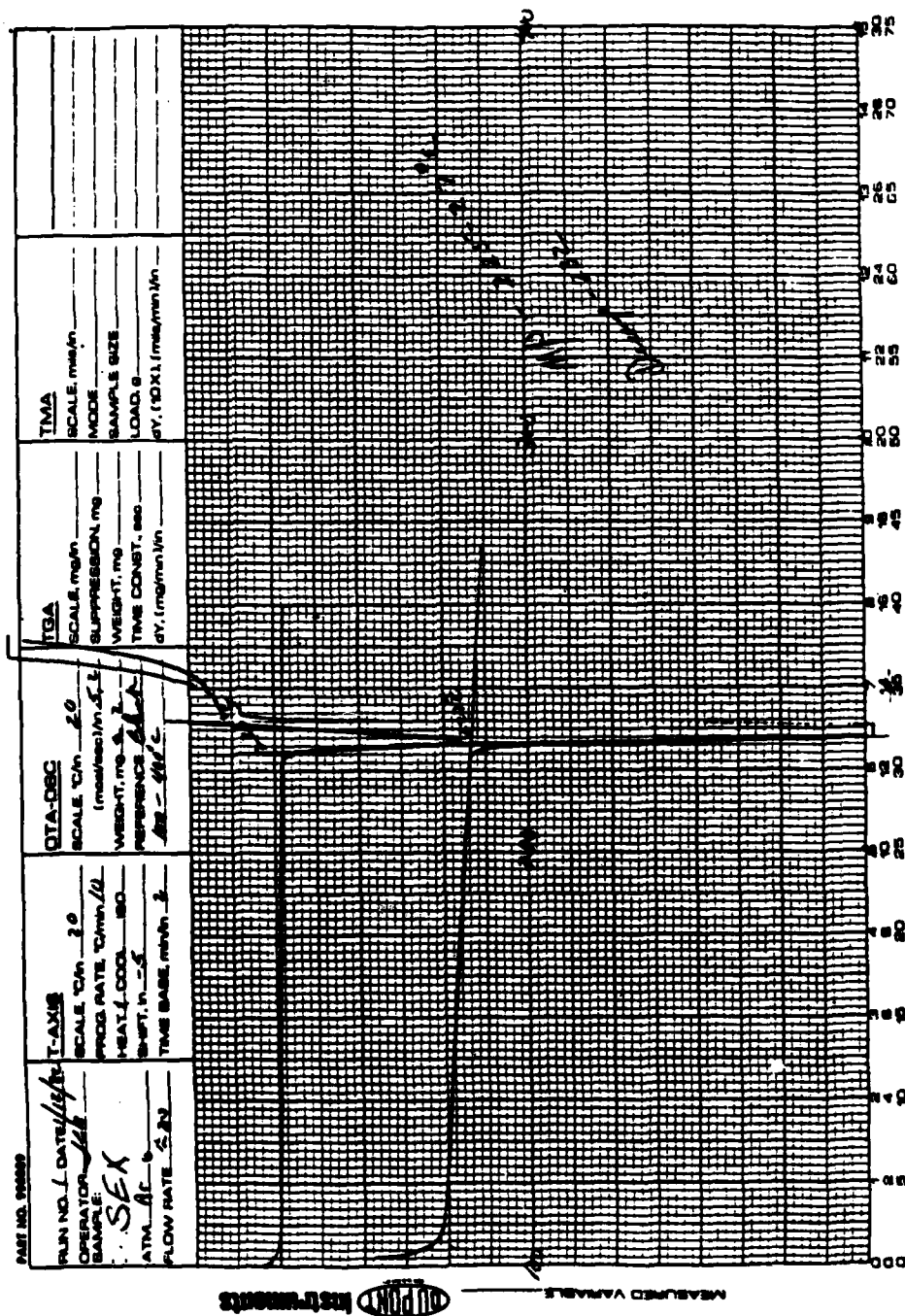
APPENDIX A



INFRARED SPECTRUM



NMR SPECTRUM



DIFFERENTIAL SCANNING CALORIMETER

APPENDIX A (concluded)

ANIMAL DATA

Species: Rabbit

Strain: New Zealand White (albino)

Source: Elkhorn Rabbitry

Sex: Male and female

Age: Young adults

Method of Randomization: Manual, Latin Square (SOP OP-STX-34)

Animals in each group: 6 animals, 3 males and 3 females

Condition of animals at start of study: Normal

Body weight range: 2.0 - 3.1 Kg

Identification procedures: Ear tattoo (SOP-OP-ARG-1)

Pretest conditioning:

1. Animals were in quarantine from 17 Dec 82 - 6 Jan 83 during which time they received sulfaquinoline in their drinking water for coccidiosis prophylaxis.
2. Animals were close clipped on 6 Jan 83. On 9 Jan 83 they were close clipped again and areas marked.

Justification: Rabbits are a proven sensitive animal model for this test.

ENVIRONMENTAL CONDITIONS

Caging: Number/cage = 1; Type of cage = stainless steel, wire mesh
bottom, battery type, no bedding, automatic flush.

Diet: Purina Certified Rabbit Chow No. 5322, approximately 110g/day
Lot numbers JUL21821F and SEPT09822A.

Water: Central line to cage battery with automatic lick dispensers

Temperature: 71 ± 1 F (22 ± 1 C)

Humidity: $50\% \pm 10\%$

Photoperiod: 0530 - 2000 hours per day (light 14 1/2 hours)

HISTORICAL LISTING OF STUDY EVENTS

Date	Day	Events
17 Dec 82	A0	Animals arrived. They were ear tattooed, weighed, sexed and held for a 2 week quarantine period.
27 Dec 82	A10	Animals weighed.
5 Jan 83	A19	Animals removed from quarantine
6 Jan 83	A20	Animals weighed and close clipped. Chemicals were randomly assigned to sites.
9 Jan 83	A23	Animals close clipped and areas marked.
10 Jan 83	0	Animals weighed and dosed.
10-31 Jan 83	0-21	Animals observed daily.
11 Jan 83	1	Bandages removed, areas scored for 24 hour post-exposure.
13 Jan 83	3	Animals scored for 72 hour post-exposure.
14,20,27,31 Jan 83	4,10,17,21	Animals weighed.
17 Jan 83	7	Animals scored for 7 day post-exposure.
23 Jan 83	14	Animals scored for 14 day post-exposure if irritation persists.
31 Jan 83	21	Animals scored for 21 day post-exposure. Study terminated.

DEVIATIONS FROM ORIGINAL PROTOCOL

1. Animals arrived on 17 Dec 82 instead of 22 Dec 82. Consequently, they were weighed on 17 Dec 82 (Day A0) and 27 Dec 82 (Day A10) while in quarantine.
2. Animals were weighed on several dates not specified in the protocol. These include 10 Jan 83 (Day 0), 27 Jan 83 (Day 17) and 31 Jan 83 (Day 21). In addition, the animals were weighed on 14 Jan 83 (Day 4) instead of 13 Jan 83 (Day 3).
3. The original protocol of 10 Nov 82 has the rabbits clipped once before dosing on 6 Jan 83 (Day A15) when removed from quarantine. The rabbits were actually clipped twice before dosing, once on 6 Jan 83 (Day A20) and again on 9 Jan 83 (Day A23). The areas were not marked until the second clipping.
4. There was an error in the addendum to the original protocol of 10 Nov 82. The date assigned to Day 10 should have been 20 Jan 83.
5. On 11 Jan 83 the humidity in the animal room was between 60 and 68% for approximately 11 hours. This slight increase in humidity should not have adversely affected the findings of this study.

Summary of Primary Skin Irritation Test Data

GLP Study No. 82006 Chemical Name _____ Conc _____ Solvent _____ Amt Applied _____ Code _____
 Date of Application 10 January 1983 SEX _____ 100% Isotonic Saline 0.5 ml TP018
 Principal Investigator Ms. Lewis

Irritation Scores

		Intact Skin Sites				Abraded Skin Sites				
Rabbit No.	Site	Erythema		Edema		Site	Erythema		Edema	
		24 hr	72 hr	24 hr	72 hr		24 hr	72 hr	24 hr	72 hr
82F271	I	0	0	0	0	II	0	0	0	0
82F272	IV	0	0	0	0	III	0	0	0	0
82F273	I	0	0	0	0	II	0	0	0	0
82F274	IV	0	0	0	0	II	0	0	0	0
82F275	IV	0	0	0	0	III	0	0	0	0
82F276	I	0	0	0	0	III	0	0	0	0
Total:		a	b	a	b		a	b	a	b
		0	0	0	0		0	0	0	0
		a+b		a+b			a+b		a+b	
		0		0			0		0	

C^I

+

0

C^A

+

0

Intact Score = $\frac{C^I}{2 \times \text{No. of Sites on test}}$ 0Abraded Score = $\frac{C^A}{2 \times \text{No. of Sites on test}}$ 0Total Score = $\frac{C^I + C^A}{2 \times \text{No. of Sites on test}}$ 0

Primary Skin Irritation Index Category I

Remarks:

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